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Gale Encyclopedia of Medicine

Paget's disease of bone

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Definition

Paget's disease of bone (*osteitis deformans*) is the abnormal formation of bone tissue that results in weakened and deformed bones.

Description

Named for Sir James Paget (1814-1899), this disease affects 1-3% of people over 50 years of age, but affects over 10% of people over 80 years of age. Paget's disease can affect one or more bones in the body. Most often, the pelvis, bones in the skull, the long bones (the large bones that make up the arms and legs), and the collarbones are affected by Paget's disease. In addition, the joints between bones (the knees or elbows, for example) can develop arthritis because of this condition.

Paget's disease is characterized by changes in the normal mechanism of bone formation. Bone is a living material made by the body through the continual processes of formation and breakdown (resorption). The combination of these two actions is called remodeling and is used by the body to build bone tissue that is strong and healthy. Strong bones are formed when bone tissue is made up of plate-shaped crystals of minerals called hydroxyapatite. Normal wear and tear on the skeletal system is repaired throughout life by the ongoing process of remodeling. In fact, the entire human skeleton is remodeled every five years.

Healthy bone tissue has an ordered structure that gives the bone its strength. Bones affected by Paget's disease, however, have a structure that is disorganized. This disorganized structure weakens the diseased bone and makes people suffering from this disease

Exhibit E

more likely to have fractures. These fractures are slow to heal.

Paget's disease of bone is most commonly found in Europe, England, Australia, New Zealand, and North America. In these areas, up to 3% of all people over 55 years of age are affected with the disease. It is interesting to note that Paget's disease is rare in Asia, possibly showing that this disease may affect some ethnic groups and geographic areas more than others.

Causes & symptoms

The cause of Paget's disease is not known. Various viruses have been suggested to be involved in this disease, but the relationship between viral infections and Paget's disease remains uncertain.

Paget's disease usually begins without any symptoms. However, as the disease progresses, bone and joint pain develop. A unique feature of Paget's disease is the enlargement of areas of affected bone. This type of enlargement is clearly identifiable on an x ray.

If the bones of the skull are affected by Paget's disease, enlargement of the skull can occur and may result in a loss of hearing. When the long bones in the legs are affected, they can become bent under the body's weight because of their weakness. Little or no injury to a bone can cause fractures in the weakened bones. Fractures that occur when no traumatic injury is present are known as spontaneous fractures.

Although rare, bone cancer can occur in less than 1% of patients with Paget's disease. Such cancer is often accompanied by an abrupt increase in the intensity of pain at the diseased site. Unfortunately, this type of cancer has a poor prognosis; the survival time is within one to three years.

Diagnosis

Paget's disease is often found when an individual is having x rays taken for medical reasons unrelated to this bone disease. A diagnosis of Paget's disease can also be made when higher than normal levels of a chemical called alkaline phosphatase are found in the blood. Alkaline phosphatase is a substance involved in the bone formation process, so if its levels are abnormally high this indicates that the balance between bone formation and resorption is upset.

Treatment

Treatment, given only when symptoms are present, consists of the following types:

Drugs

aget's disease is most often treated with drug therapy, with bone ain lessening within weeks of starting the treatment. While onsteroidal anti-inflammatory drugs can reduce bone pain, two dditional categories of drugs are used to treat this disease; they are escribed below.

lormone treatment

he hormone calcitonin, which is made naturally by the thyroid land, is used to treat Paget's disease. This compound rapidly ecreases the amount of bone breakdown or loss (resorption). After pproximately two to three weeks of treatment with calcitonin, bone ain lessens and new bone tissue forms. Calcitonin is commonly iven as daily injections for one month, followed by three injections ach week for several additional months. The total dose of calcitonin iven to an individual depends upon the amount of disease present nd how well the individual's condition responds to the treatment.

lthough calcitonin is effective in slowing the progression of Paget's isease, the favorable effects of the drug do not continue for very ong once administration of the drug is stopped. In addition, some emporary side effects can occur with this drug. Nausea and flushing re the most common side effects and have been found in 20-30% f individuals taking calcitonin. Vomiting, diarrhea, and abdominal ain can also occur, but these effects are also temporary. A form of alcitonin taken nasally causes fewer side effects, but requires higher oses because less of the drug reaches the diseased bone.

isph sph nates

he bisphosphonate group of drugs are drugs that bind directly to one minerals because of their specific chemical structure. Once ound to the bone, these drugs inhibit bone loss by reducing the ction of bone cells that normally degrade bone during the emodeling process. Unlike treatment with calcitonin, the positive ffects of increased bone formation and reduced pain can continue or many months or even years after bisphosphonate treatment is topped. Bisphosphonates are considered the treatment of choice for aget's disease and are usually given for 3-6 months at a time.

isphosphate drugs suitable for the treatment of Paget's disease are tidronate, pamidronate, alendronate, clodronate, and tiludronate. ther bisphosphonate drugs are under development as well. The nain side effects of these drugs include a flu-like reaction pamidronate), gastrointestinal disturbances (alendronate, lodronate), and abnormal bone formation (etidronate, when taken n high doses).

Surgery

reatment of Paget's disease usually begins with drug therapy. lowever, various surgical treatments can also be used to treat keletal conditions that occur in patients with Paget's disease.

n patients with severe arthritis of the hip or knee, a joint eplacement operation can be beneficial. Notably, in addition to the nalformation of bone tissue caused by this condition, there are reater numbers of blood vessels that also form in the diseased one, making surgery to bones affected with Paget's disease more ifficult.

Prognosis

here is no cure for Paget's disease. However, the development of otent bisphosphonate drugs like alendronate and pamidronate has esulted in the ability to slow the progress of the disease.

Key Terms

Bisphosphonate
A class of drugs used to treat Paget's disease. These drugs bind to the minerals in bone tissue and lessen the amount of bone loss associated with Paget's disease.

Calcitonin
A naturally occurring hormone made by the thyroid gland that can be used as a drug to treat Paget's disease.

Remodeling
The ongoing process of bone formation and breakdown that results in healthy bone development.

Further Reading

For Your Information

Books

- Krane, Stephen M. "Paget's Disease of Bone." In *Harrison's Principles of Internal Medicine,* edited by Anthony S. Fauci, et al. New York: McGraw Hill, 1998, pp. 2266-2269.

Periodicals

- "Bone Pain in the Elderly." *Generations* 20 (Winter 96/97): 39.
- Delmas, Pierre D., and Pierre J.Meunier. "The Management of Paget's Disease of Bone." *New England Journal of Medicine* 336 (February 20, 1997): pp. 558-566.
- "Paget's Disease: Skeletal Deformity with or without Pain." *Geriatrics* 51 (June 1996): 50.
- Sadovsky, Richard. "Paget's Disease of the Bone: Bisphosphonate Treatment." *American Family Physician* 55 (March 1997): 1400.

Organizations

- The Paget Foundation. 120 Wall St., Suite 1602, New York, NY

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